I. AMENDMENTS

Applicants respectfully request entry of the amendments filed June 25, 1996 in connection with the parent application, U.S. Serial No. 08/169,293.

II. REMARKS

Claims 1-31 were examined in connectioin with the parent application. Two substantive examinations ("Office Actions") issued in the parent application,namely, the July 12, 1995 Office Action and the March 5, 1996 Office Action ("March 5, 1996 Office Action"). In the March 5, 1996 Office Action, the specification was objected to and the claims were rejected as follows: (1) the specification was objected to and claims 1-12 and 14-31 remain rejected under 35 U.S.C. § 112, first paragraph; (2) claims 1-23 and 31 remain rejected under 35 U.S.C. § 112, second paragraph; claims 1-17 and 19-23 remain rejected under 35 U.S.C. § 103 for allegedly being obvious in view of Aldrovandi et al. (Nature 363:732-736 (1993); "Aldrovandi") taken with Pinto et al. (J. Leukocyte Biol. 49:579-586 (1991); "Pinto"), that claim 18 has been rejected under 35 U.S.C. § 103 as allegedly unpatentable over Aldrovandi and Pinto in view of Bernstein et al. (J. Clin. Invest. 88:540-545(1991); "Bernstein"), that claims 24-30 have been rejected under 35 U.S.C. § 103 as allegedly unpatentable over Berenson et al. (Blood 77:1717-1722 (1991); "Berenson") and Baum et al. (Proc. Natl. Acad. Sci. 89:2804-2808 (1992); "Baum") taken with Pinto and that claim 31 has been rejected under 35 U.S.C. § 103 as allegedly unpatentable over Baum taken with Pinto. In view of the following remarks, Applicants respectfully request the Examiner to reconsider and withdraw these rejections.

35 U.S.C. § 112, First Paragraph

Claims 1-12 and 14-31 remain rejected under 35 U.S.C. § 112, first paragraph.

In the March 5, 1996 Office Action, the specification was objected to and claims 1-12 and 14-31 are rejected under 35 U.S.C. § 112, first paragraph. Regarding claims 1-12 and 14-31, the Office contended that these claims must be limited to a non-human animal because the specification allegedly fails to provide the guidance necessary to show that the invention would work in humans. In one instance, the Office asserted that the specification allegedly fails to provide guidance regarding the routes of administration, amount, time course, and number of treatments, which are alleged to be required to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation. The Office also asserted that the relationship between HIV infection and macrophage depletion is not elucidated in the specification and that HIV infection in conjuction with Cl_2MDP ("DMDP) treatment would appear to result in depletion, not prevention of depletion, of non-autologous hematopoietic cells.

Applicants respectfully traverse.

Prior to addressing the merits of claims 1-12 and 14-31, Applicants note that claim 19 is directed to a non-human mammal comprising human hematopoietic cells wherein the mammal contains a decreased level of endogenous macrophages sufficient to prevent depletion of non-autologous hematopoietic cells. Claims 20 through 23 are variously dependent on claim 19. Applicants respectfully request that the Office remove the above ground for rejection against claims 13 and 19-23, which as filed are limited to non-human animals.

Regarding claims 1-12 and 14-18 and 24 to 31, Applicants submit and reassert their position that the specification does in fact teach how to make and use the invention for human therapies. Page 7, lines 7 through 19 of the specification states that endogenous macrophages can be depleted by treatment with L-leucine methyl ester, by the administration of colloidal carbon to the reticuloendothelial systems or by the administration of liposome-encapsulated DMDP. On page 10, line 3 through page 12, line 6, and Example 6 of the specification, Applicants teach that typically, DMDP is administered in a manner whereby it is taken up by

macrophages but not other cells types, for example, by encapsulation in liposomes. How to make and use liposome-encapsulated DMDP is well known in the art at the time the invention was made as described in the specification and the Office's cited reference Pinto et al., (1991) J. Leukocyte Biol. 49:579–586, and reference 33 cited therein. Example 6 of the application teaches that liposome-encapsulated drug administered intravenously will produce this effect. An effective amount is taught in the specification to be from 5 to 10 ml of liposomes per kg of human body weight.

Therefore, the specification enables the route of administration (intravenously) and the amount (5 to 10 ml per kg of human weight). The specification further teaches that "an effective amount" can be empirically determined using monitoring methods well known to those of skill in the art (see page 11, line 12 to line 23 of the specification). Therefore, the number and time course of treatment can be easily determined by monitoring non-autologous macrophages using well known methods. Additionally, the specification provides examples of the number and time course of treatments in Examples 7 through 9 of the application. Accordingly, the specification in combination with information known in the art, teaches how to make and use the invention as far as the claims read on human therapies.

Furthermore, the SCID-hu mouse was already a well-accepted model for human disease at the time the invention was made. For example, Kaneshima et al., (Proc. Natl. Acad. Sci. 88:4523-4527 (1991)), a copy of which is attached hereto, describes the use of SCID-hu mice to study various parameters of HIV infection in humans. In this study, SCID mice were engrafted with human lymph nodes, and the resulting SCID-hu mice were subsequently infected with HIV isolates derived freshly from patients. The engrafted human lymph nodes were examined histologically for HIV infection and the animals were analyzed at various time points after infection for viremia. The results showed that these mice became infected with HIV, and the same target cells -- namely the T-lymphoid and monocytic lineages -- were infected as in HIV-infected humans. (page 4524, column 2, paragraph 2; page 4526, column 1, Figure 3; page 4524, column 2, paragraph 1; page 4525, Figure 2). Furthermore, when these mice were treated with

3'-azido-3'-deoxythymidine (AZT) or 2',3'-dideoxyinosine (ddIno) before HIV infection, and in dose ranges similar to those used in man, infection and viremia were later suppressed in a dose-dependent manner. (page 4525, column 2, paragraph 1 and bridging paragraph of pages 4525 and 4526; page 4526, column 2, Figure 5). Thus, effective dosages of a therapeutically effective drug are capable of extrapolation from the SCID-hu mouse model to humans.

In addition, DMDP had already been used in humans at the time the invention was made. Martoni et al. (1991) Oncology 48:97-101 ("Martoni") and Bickerstaff et al. (1990) J. Bone Joint Surg. 72-B:132-136 ("Bickerstaff"), copies attached. In Martoni, a controlled clinical study is described in which DMDP was administered in conjunction with specific antitumor treatment to patients with breast carcinoma that had metastasized to the skeleton in an attempt to stem osteoporosis. Dosages and routes of administration for DMDP are given. (page 98, column 1, paragraph 1). In Bickerstaff, DMDP was used to treat patients with Paget's disease for prevention of osteopenic changes. Dosages and routes of administration for DMDP are given. (page 133, column 1, paragraph 2).

In view of Kaneshima, and given the guidance in Martoni and in Bickerstaff, then, one of ordinary skill in the art could reasonably be expected to be able to determine therapeutically effective dosage ranges of DMDP humans.

The Office asserted that the relationship between HIV infection and macrophage depletion is not elucidated in the specification and that HIV infection in conjuction with DMDP treatment would appear to result in depletion, not prevention of depletion, of non-autologous hematopoietic cells. Applicants point out that the methods of this invention are particularly useful when the animal is immunocompromised (claims 7, 20 and 24). An animal may become immunocompromised due to radiation therapy (claim 10), chemotherapy (claim 11) or from infection with HIV (claims 8 and 25). Thus the relevant relationship is between HIV infection and immunosuppression, not HIV infection and the number of macrophages.

Regarding claims 10 and 11, the Office has asserted that these claims must be limited to DMDP treatment on the ground that radiation therapy and chemotherapy could, under certain

circumstances, possibly ablate the entire endogenous immune system, rendering DMDP treatment moot. Applicants traverse on several grounds. The standard for enablement does not rest on the requirement that the claimed invention be applicable in all possible situations. Indeed, the Office addressed situations in which the invention is not called for (i.e., not indicated) because the desired result (i.e., depletion of macrophages) has already occurred. A claimed invention does not become unpatentable simply because there may be instances where the invention may not be required or indicated. The Office's own qualified language, that radiation therapy and chemotherapy could possibly ablate the entire endogenous immune system, itself acknowledges that the invention is indeed applicable in other instances besides the attenuated one postulated.

The Office further contended that the specification "fails to provide guidance to one of ordinary skill regarding the types and protocols of chemotherapy or radiation therapy which would transiently immunocompromise the host immune system and yet allow the DMDP treatment to kill macrophages." (Page 3 of March 5, 1996 Office Action). Methods of radiotherapy and chemotherapy are well-known in the art and need not be taught in the specification. Applicants are not required to provide information known to one of skill in the art at the time the application was filed. See, e.g., In re Buchner, 18 USPQ2d 1331 (Fed. Cir. 1991) ("The specification need not disclose what is well known in the art."). Because there are innumerable chemotherapy and radiation protocols known in the art, this requirement has been met.

The Office also noted that the specification fails to provide guidance as to the interaction of radiation/chemotherapy with DMDP treatment. As discussed above, the problem of rapid clearance of non-autologous hematopoietic cells occurs even if an animal is immunocompromised. Applicants made this observation in such a system (the SCID mouse). Page 5, lines 29-34; Examples 6 and 8. Treatment with DMDP prevents the rapid clearance of non-autologous hematopoietic cells in SCID mouse. Thus, it is not unreasonable to apply the method of preventing depletion of non-autologous hematopoietic cells by decreasing the number

of macrophages to an immunocompromised host, regardless of the mechanism by which the host is immunocompromised, e.g., due to radiation or chemotherapy.

The Office went on to state that "[t]he known methods of radiation and chemotherapy ablate dividing cells and therefore ablate all mature, immature and progenitor cells and would therefore ablate the macrophages as well." (Page 3 of June 12, 1995 Office Action). Applicants respectfully point out that regimens of radiation therapy and chemotherapy vary widely and the conclusory statement that these methods "would ablate all mature, immature, and progenitor cells" simply does not reflect the typical situation. Further, even if in certain rare instances macrophages were ablated by radiation therapy or chemotherapy, this does not render the claimed invention unpatentable under 35 U.S.C. § 112, first paragraph. Rather, as the Office indicated, such an instance might merely render the claimed invention "moot".

The Office also stated that the specification "fails to present evidence that the combination of systems [radiation/chemotherapy and macrophage depletion] would result in depletion of macrophages." The Office has failed to provide proof that one of skill in the art would doubt the truth or accuracy of the claimed invention. This burden has not been met. Moreover, in the Examples, an immunocompromised animal (SCID) is provided with non-autologous hematopoietic cells (SCID-hu thy/liv) in the presence or absence of endogenous macrophages (+/- DMDP) and is found to sustain non-autologous hematopoietic cells better in the absence of endogenous macrophages. Based on these observations, it is reasonable and credible to believe the truth and accuracy of the invention as broadly claimed.

Regarding claim 31, the Office contended that the specification fails to define ablating "in whole or in part" the endogenous stem cell population of the host animal. In the Applicant's Amendment and Response to Final Office Action (June 25, 1996), claim 31 was amended to remove the phrase "in whole or in part". Entry of this Amendment was entered as noted in the Advisory Action issued on July 15, 1996 in the parent application (Serial No. 08/169,293).

In view of the preceding remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, Second Paragraph

The Office has maintained the rejection of claims 1 to 23 under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter of the invention. The Officed opined that the terms "in whole or in part" and "substantially" are vague and unclear.

Without conceding the correctness of the Examiner's position, and merely to place the claim in condition for allowance, the phrase "in whole or in part" has been deleted from the claim. Affirmation of this claim amendment has been made herein. In view of the amendment to the claim, Applicants respectfully request that the rejection of claim 31 under 35 U.S.C. § 112, second paragraph, be removed.

However, Applicants maintain their position that the term "substantially" is definite to apprise those of skill in the art of the invention of the rejected claims.

It is well-settled law that the mere use of an adverb such as "substantially" will not render a claim indefinite and invalid for allegedly failing to meet the requirements of the second paragraph of 35 U.S.C. § 112 (*See, e.g., In re Mattison and Swanson*, 184 U.S.P.Q. 484, 486 (CCPA 1975)) (holding that the claim phrase "substantially increase" was not indefinite under § 112 and that an applicant's specification is not required to teach percentage of increase). Rather, claims using an adverb such as "substantial" are sufficiently definite if, when read in light of the specification, it will distinguish the claimed invention from the prior art and reasonably apprise those skilled in the art how to make and use the invention. *See, e.g. Rosemount, Inc. v. Beckman Instruments, Inc.*, 221 U.S.P.Q. 1 (Fed. Cir. 1988) (holding that one of skill in the relevant art would know what the claim term "substantially equal" delineates).

The definiteness requirement of § 112, second paragraph only requires that the claim be as precise in language as the relevant technology permits. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied,* 480 U.S. 947 (1987), wherein the Federal Circuit held that claim language describing antibodies having

affinity of "at least about" 10^8 liters/mole was not indefinite because, read in light of the specification, a skilled artisan in the antibody field would be reasonably apprised of the claimed subject matter. The present invention is claimed as a method to "substantially" prevent depletion of non-autologous hematopoietic cells. The specification teaches various methods to perform the method and defines "substantial" on page 11, lines 3 to 11. Accordingly, claims 1 to 23 are not indefinite. Applicants request withdrawal of this rejection.

35 U.S.C. § 103

Claims 1-17 and 19-23 remain rejected under 35 U.S.C. § 103 as allegedly unpatentable over Aldrovandi taken with Pinto; claim 18 remains rejected under 35 U.S.C. § 103 as allegedly unpatentable over Aldrovandi and Pinto in view of Bernstein; claims 24-30 remain rejected under 35 U.S.C. § 103 as allegedly unpatentable over Berenson and Baum taken with Pinto; and claim 31 remains rejected under 35 U.S.C. § 103 as allegedly unpatentable over Baum taken with Pinto.

The traversal of the rejection is maintained by Applicants. In support of the arguments presented below, Applicants' undersigned attorney submits herewith the Declaration of Ben Chen, a coinventor of the subject application and one of skill in the art at the the application was filed.

Aldrovandi teaches the use of the SCID-hu mouse as a possibly useful *in vivo* system for the study of HIV-1-induced pathology. Aldrovandi shows results of experiments which involve human fetal liver and thymus transplants which were later shown to be capable of being infected by HIV-1. Notably, Aldrovandi also teaches that human fetal Thy/Liv cells can be successfully transplanted in SCID mice. Aldrovandi does not address or suggest the problem of rapid depletion of non-autologous hematopoietic cells; it does not discuss or suggest any relationship between a SCID-hu system and the problem of rapid depletion of non-autologous hematopoietic cells or a means to prevent it.

Pinto describes the prominent role of macrophages in host resistance to pathogenic microorganisms. Applicants maintain their position that Pinto merely discloses the effects of DMDP encapsulated in liposomes on antimicrobial resistance, particularly against infection with *Listeria monocytogenes* and herpes simplex virus type 2. Pinto does not address and therefore does not provide a solution to the problem of clearance of non-autologous hematopoietic cells.

However, the Office argued that because DMDP was found to decrease the number of endogenous macrophages and the results of a decreased number of macrophages would be expected to be numerous in view of the major role of macrophages in maintaining the immune response, the claimed invention is obvious. Applicants respectfully disagree.

While the role of macrophages in maintaining the immune response may be numerous, it was heretofore unknown that decreasing the number of macrophages would prevent depletion of non-autologous hematopoietic cells. The Office's position appears to be that one would expect this result without providing the requisite teaching or suggestion of such in the cited art. For this reason, Applicants submit that the references fail to teach or suggest the inventions of the claims because the art fails to teach or suggest the intellectual and technical leap as proffered by the Office in framing the rejection of the claims under 35 U.S.C. § 103.

In support of the foregoing arguments, Applicants cite the following publications. Marcus et al. (1996) Transplantation 61:777-783 ("Marcus"); Pflumio et al. (1993) International Immunology 5:1509-1522 ("Pflumio"); and Shpitz et al. (1994) J. Immunol. Methods 169:1-15 ("Shpitz").

In Marcus, the authors address the problem of low engraftment of allogeneic and xenogeneic cells in SCID mice. The publication describes the transfer into two strains of SCID mice -- C3H/SCID and C.B-17/SCID -- of allogeneic and xenogeneic cells. Allogeneic C.B-17/SCID bone marrow cells were engrafted poorly compared with syngeneic C3H/SCID when transplanted into C3H/SCID recipients, whereas cells of both strains were equally well engrafted into C.B-17/SCID mice. (page 779, column 1, Table 2). One month after transplantation of C3H/SCID and C.B-17/SCID mice with human 70 x 10^6 peripheral blood lymphocytes, the total

human Ig was 199.8 ± 46.2 μg/ml in the C3H/SCID mice compared with 1360 ± 341.1 μg/ml in the C.B-17/SCID mice group. (page 781, column 2, paragraph 2, lines 2-7). C.B-17/SCID mice were much more permissive for out-growth of human Burkitt lymphoma (Raji) cells. (bridging paragraph of pages 780 and 781). The resistance to human Raji cells exhibited by C3H/SCID mice could be adoptively transferred by infusion of C3H/SCID splenocytes into C.B-17/SCID mice. (page 781, column 2, paragraph 3 and page 781, column 1, Figure 3). The authors conclude that the marked immunoreactivity against foreign grafts is mediated by non-T non-B mechanisms, (page 782, column 1, paragraph 1, lines 7-9) and point toward NK cells as the cells possibly responsible for low engraftment levels (page 782, column 1, lines 12-17).

The results reported in Marcus show that, at the time of publication of the reference, it was unclear precisely which cell population(s) or other factor(s) are responsible for rejection of non-autologous cells in engrafted SCID mice. The authors suggest that, since SCID mice lack $CD4^+$ and $CD8^+$ T cell function, these mice provide relevant models for studies of non-T cell, non-B cell mechanisms of allograft or xenograft rejection. (page 782, bridging paragraph of columns 1 and 2). The authors suggest that another population, perhaps NK cells, are the mediators of the rejection in SCID mice, but were unable to point conclusively toward any one cell type. (page 782, column 1, paragraph 3, lines 6-12). Therefore, it would not have been obvious to one of ordinary skill in the art to deplete macrophages in order to avoid rejection of non-autologous cells by SCID mice engrafted with human hematopoietic cells.

In Pflumio, the authors of the publication address the problem of low engraftment of murine tissues with functional human T and B cells when adult SCID mice are engrafted with human lymphoid tissue. Newborn SCID mice were injected with human bone marrow and peripheral blood leukocytes. Newborn SCID mice were specifically chosen as recipients for human cell engraftment because natural killer cell activity and other immune functions do not develop until several weeks after birth. (page 1510, column 1, paragraph 2). The extent of human cell engraftment was measured by probing blots of EcoRI-cut and electrophoresed DNA for the presence of human α-satellite DNA. The functionality of engrafted cells was assessed by

measuring the concentration of human immunoglobulin in the serum and monitoring the frequency of symptoms resembling graft-versus-host disease (GVHD). The results showed that human cells spread to many organs. (page 1511, column 2, paragraph 4, lines 10-13; page 1512, Figure 1; page 1513, column 1, Figure 2). In addition, many mice exhibited GVHD-like symptoms: these mice became sick within 2-4 weeks following transplantation, and histological analyses of organs with human lymphoid infiltrates revealed patterns of tissue destruction consistent with GVHD. (pages 1518 and 1519, Figure 7; page 1517, column 1, lines 6-9 and 18-26). This fact, coupled with the presence of human IgG and IgM antibodies (page 1516, column 1, Figure 5; page 1516, column 2, paragraph 1), indicated that the engrafted human cells retained some immune functions.

The results reported in Pflumio show that, contrary to the Office's position that it would have been obvious to one of ordinary skill that depleting macrophages would prevent rejection of non-autologous cells in engrafted SCID mice, the population(s) of cells responsible for such rejection was in fact unknown in 1993. The authors reported that, compared with the literature on the use of adult SCID mice as recipients, the transplanted cell dose using newborn SCID mice was much lower and the human cell infiltration of the mouse hematopoietic and non-hematopoietic organs was more extensive. (page 1510, column 2, paragraph 1, lines 4-8; page 1518, column 1, paragraph 1, lines 1-12). Since newborn SCID mice lack the NK cell function of adult SCID mice, the authors suggested that NK cells were perhaps the mediators of rejection in adult SCID mice, but did not draw any firm conclusions as to the identity of the cell type involved. (page 1510, column 1, paragraph 2, lines 2-8; page 1518, column 2, lines 3-11).

In Sphitz, the authors address the problem of low and variable short term human peripheral blood lymphocyte (PBL) engraftment in SCID mice, noting that, in addition to showing low levels of engraftment, human T cell engraftment in the lymphoid organs of hu-PBL-SCID mice is significantly limited during the early post-reconstitution period, as the human PBLs appear to remain predominantly in the peritoneal cavity. (page 2, column 1, paragraph 1, lines 17-29). To overcome these problems, various treatment protocols were pursued. The mean

level of $CD3^+$ cells in the spleen was < 5% in untreated SCID mice injected with human PBLs. Depletion of mouse NK cells by pre-treatment with anti-asialo G_{M1} rabbit polyclonal antibody resulted in a marginal improvement of short term reconstitution with human $CD3^+$ cells, while preirradiation with 3 Gy improved reconstitution to over 16% $CD3^+$ cells on days 12-14 following engraftment. However, when a combination of pretreatment with anti-asialo G_{M1} plus irradiation was pursued, the mean percentage of human $CD3^+$ cells in the spleen increased to 40% within 2 weeks following injection of PBLs. (page 5, Figure 1; bridging paragraph of pages 4 and 6). The human immune cells in these mice were shown to be functional by the *in vivo* demonstration of an appropriate secondary immune response to the injection of tetanus toxoid (page 9, bridging paragraph of columns 1 and 2, and bridging paragraph of pages 9 and 10; page 9, column 2, Figure 5) and by an *in vitro* proliferative response to phytohemagglutinin. (page 9, column 1, Table 4). The authors postulated that the role of anti-asialo G_{M1} treatment in the successful engraftment of human PBLs was reduction in endogenous NK activity in SCID mice. (page 13, column 1, paragraph 1, lines 6-10). The mechanism by which preirradiation of SCID mice improves engraftment with human PBLs was stated to be unknown. (page 13, column 1, paragraph 1, lines 4-6).

The results reported in Shpitz show that, contrary to the Office's assertion that it would have been obvious to one of ordinary skill to deplete macrophages in order to prevent depletion of non-autologous cells in engrafted SCID mice, the cell type responsible for the poor engraftment was unknown, even at the time of publication of Shpitz. The authors observed that pretreatment with anti-asialo G_{M1} plus γ-irradiation resulted in increased numbers of functional human $CD3^+$ cells in the spleen, and attributed the increase to a reduction in the NK cell population. (page 13, column 1, paragraph 1, lines 1-10).

Taken together, the teachings of Marcus, Pflumio and Shpitz show that, at the time the application describing the present invention was filed, the teachings of the art did not identify which cell population(s) or which other factor(s) are the mediators of non-autologous cell

depletion in engrafted SCID mice. Accordingly, it would not have been obvious to try reduction of the macrophage population as a means of obviating such depletion.

Reconsideration and removal of this rejection is respectfully requested.

Claim 18 remains rejected under 35 U.S.C. § 103 as allegedly unpatentable over Aldrovandi and Pinto in view of Bernstein. The Office asserted that Bernstein discloses that LPS upregulates HIV expression by macrophage growth factors. The Office has asserted that, in view of Bernstein's disclosure that macrophages are latent HIV reservoirs, it would have been obvious to the ordinary artisan to deplete macrophages in order to reduce the viral reservoirs.

Applicants maintain their traversal. Claim 18 is to a method of treating an immunocompromised animal which includes administering an effective amount of non-autologous hematopoietic cells and decreasing endogenous macrophages. Applicants reassert and incorporate by reference their position with respect to Aldrovandi and Pinto. Aldrovandi and Pinto do not, either alone or in combination, disclose or suggest a method of treating an immunocompromised animal, or administering non-autologous hematopoietic cells in conjunction with decreasing endogenous macrophages. In addition, for the reasons provided above, there is no motivation to combine the references, and even if the references were combined, the references would not teach or suggest the invention. Pinto disclosed that DMDP reduces microbial resistance in mice by reducing the number of macrophages. In light of the failure of Aldrovandi and Pinto to render the claimed invention unpatentable, subsequent references cannot make up the deficiency.

Even if a combination of references based on the motivation to practice an invention other than, and unrelated to, the claimed invention were proper, the rationale given here is not even scientifically credible. Bernstein discloses that activation of monocyte-derived macrophages with lipopolysaccharide (LPS) decreases HIV replication. Given this, the Office's statement that it would be obvious to "inactivate macrophages as a method of treatment in order to abolish viral replication" is without support. Moreover, Applicants' method is not a method of treating HIV infection, it is to treating an immunocompromised animal, the compromised state

being the result of HIV infection. In view of the following remarks, reconsideration and withdrawal of this rejection are respectfully requested.

The rejection of claims 24 to 30 under 35 U.S.C. § 103 as allegedly unpatentable over Berenson and Baum taken with Pinto has been maintained. The rejection of claim 31 as allegedly obvious over Baum taken with Pinto has also been maintained.

Applicants reassert and incorporate by reference their position with respect to Pinto.

As noted above, the invention of the claims is not the result of immunosuppression. SCID-hu mice (inherently immunosuppressed) also showed depletion of administered PBLs 72 hours after administration. In contrast, treated SCID-hu mice showed a marked maintenance of non-autologous PBLs 72 hours after administration (see Figures 1 and 2). Therefore, the teaching of Pinto regarding immunosuppression do not address or explain this result. The addition of Berenson and Baum do not overcome the deficiency present in Pinto. Accordingly, the combination of the references do not teach, suggest or enable the invention of claims 24 to 31. For these reasons, the combination of prior art fails to teach or suggest the invention of the claims under 35 U.S.C. § 103. Applicants request that the 35 U.S.C. § 103 rejections not be reinstated in the file wrapper application.

III. CONCLUSION

If a telephone interveiw would be of assistance in advancing prosecution of the above-identified application, the Examiner is invited to telephone the undersigned at the number provided below.

Applicants submit that all issues addressed in the Office Action issued in the underlying application have been properly disposed of in this response. Accordingly, a Notice of Allowance is believed to be in order and the early mailing thereof would be greatly appreciated.

No fee is deemed necessary in connection with the filing of this paper. However, if the Patent Office determines that an extension and/or other fee is required, Applicants petition for

any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions an/or other fees due in connection with the filing of this document to our Deposit Account No. 03-1952 (**Our Ref. No. 20296-20013.01**). However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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